CAMO (COMPARING ANIMAL MODELS TO ORGANOIDS) - TESTING MEDICAL COUNTERMEASURES WITH MICROPHYSIOLOGICAL SYSTEMS AND COMPARING TO TRADITIONAL ANIMAL MODELS AND CLINICAL TRAILS

Use Of Animal OTEs To Determine The Appropriate Model Species For Mcm Development

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In drug development, achieving FDA approval is dependent upon using an animal model most representative of the human response. Therefore, knowing which species to use prior to initiating pivotal studies can greatly improve the chance of MCM approvals. To address this problem, in a project funded by Defense Threat Reduction Agency (DTRA), we have developed Organ Tissue Equivalents (OTEs) from several species commonly used in toxicological research and compared their responses with human derived OTEs when challenged with a variety of drugs.

In this study we developed liver, lung and small intestine OTEs from Human, Mouse, Rat, Dog, and non-human primate. Each OTE was constructed from of primary cells representing the main cell types and proportions normally found in that organ. For liver: Hepatocytes, Stellate, Kupffer, Endothelial and cholangiocyte cells; for lung: bronchial epithelial, fibroblasts, microvascular endothelial and macrophage cells; for intestine: enterocytes, enteroendocrine, goblet, paneth, and stem cells. All 15 OTE types remained viable and for a minimum of one month. In addition to viability, they were extensively characterized by immunohistochemistry for structural integrity, basic immune response by cytokine release when stimulated, ability to metabolize drugs such as diazepam, opioids and VX (in the case of the Liver OTEs) formation of ciliated epithelia and mucus release (in the case of lung OTEs).

After this in-depth characterization, the EC50 values for 6 drugs (cisplatin, Arsenic, diazepam, propranolol, Acetaminophen and Aflatoxin B1) was determined for all 15 OTEs. Serial dilutions of the drugs were allowed to react with the OTEs for 72 hrs. and viability assessed by intracellular ATP levels. Analyzing the results showed that there were clear specific differences between some drugs and organs. For example, it is known that Aflatoxin elicits acute toxicity in human liver, but mice are far more resistant to its effects due to their ability to rapidly inactivate the epoxide metabolites produced. This can be clearly seen in the species liver OTEs where Human, Rat, and primate livers are more than 20x more sensitive to aflatoxin B1 than are mouse liver OTEs.

Having established and verified this system of OTEs, one further critical question that we are pursuing is “do these species OTEs faithfully represent what is happening in vivo?”. To address this point, we are developing a physiologically more relevant higher throughput, integrated multi-organoid system on a chip. Such a system will allow us to better visualize inter-organ communication such as pro-drug activation, multi-drug interactions, and signaling between healthy and diseased tissue.

The next step will be to use this multi-organ micro-physiological platform to further validate the system by comparing results obtained in vitro with published data obtained using animal models. Such comparisons could include simple drug screens, toxicity testing disease modelling and viral pathogen screens. Ultimately, we intend integrating full immune system which will take us to the next level of sophistication. With 15 such well characterized OTEs from multiple animal species, and the combined expertise in our institute we feel we are in a unique position to take the nest step forward.

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